Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Preclinical Evaluation of Pulsed Field Ablation

Electrophysiological and Histological Assessment of Thoracic Vein Isolation

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BACKGROUND: Pulsed field ablation (PFA) is a uniquely tissue-selective, nonthermal cardiac ablation modality. Delivery parameters such as the electrical waveform composition and device design are critical to PFA's efficacy and safety, particularly tissue specificity. In a series of preclinical studies, we sought to examine the electrophysiological and histological effects of PFA and compare the safety and feasibility of durable pulmonary vein and superior vena cava (SVC) isolation between radiofrequency ablation and PFA waveforms.

METHODS: A femoral venous approach was used to gain right and left atrial access under general anesthesia in healthy swine. Baseline potentials in right superior pulmonary and inferior common vein and in SVC were assessed. Bipolar PFA was performed with monophasic (PFA_{Mono}) and biphasic (PFA_{Bi}) waveforms in 7 and 7 swine sequentially and irrigated radiofrequency ablation in 3 swine. Vein potentials were then assessed acutely, and at ≈10 weeks; histology was obtained.

RESULTS: All targeted veins (n=46) were successfully isolated on the first attempt in all cohorts. The PFA_{Bi} waveform induced significantly less skeletal muscle engagement. Pulmonary vein isolation durability was assessed in 28 veins: including the SVC, durability was significantly higher in the PFA_{Bi} group (18/18 PFA_{Bi}, 10/18 PFA_{Mono}, 3/6 radiofrequency, P=0.002). Transmurality rates were similar across groups with evidence of nerve damage only with radiofrequency. Pulmonary vein narrowing was noted only in the radiofrequency cohort. The phrenic nerve was spared in all cohorts but at the expense of incomplete SVC encirclement with radiofrequency.

CONCLUSIONS: In this chronic porcine study, PFA-based pulmonary vein and SVC isolation were safe and efficacious with demonstrable sparing of nerves and venous tissue. This preclinical study provided the scientific basis for the first-in-human endocardial PFA studies.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: atrial fibrillation ■ catheter ablation ■ endocardium ■ phrenic nerve ■ pulmonary vein

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WHAT IS KNOWN?

- Pulsed field ablation (PFA) leads to cell death by irreversible electroporation.
- Myocardial cells have a greater sensitivity to PFA compared with nerves, arteries and the esophagus, making it an attractive energy modality for pulmonary vein and atrial ablation.
- Prior reports have reported on pulmonary vein ostial tissue and atrial ablation but have not demonstrated feasibility and durability of pulmonary venous isolation.

WHAT THE STUDY ADDS?

- We demonstrate the safety, efficacy, and durability of achieving catheter-based electrical isolation of pulmonary veins using optimized monophasic and biphasic PFA waveforms and describe procedural and histological characteristics of PFA in swine atrial tissue.
- Both waveforms created confluent myocardial lesions that demonstrated a myocardial-specific ablative effect.
- Biphasic PFA was more durable than monophasic PFA and radiofrequency ablation lesions.

Many advances have been made over the past decade to improve the safety, efficacy, and efficiency of pulmonary vein (PV) isolation to treat atrial fibrillation. Among these, endocardial pulsed field ablation (PFA) is particularly attractive because its nonthermal ablative mechanism exhibits specificity for myocardial tissue.[1–3] PFA has the potential to completely avoid the collateral injury attendant with all other contemporary thermal energy sources.[4–9] A custom PFA generator with optimized pulse characteristics has been shown to be safe and effective in the clinical setting.[1,3] Herein, we describe a precedent preclinical study comparing electrophysiological and histopathologic features of PFA using monophasic (PFA_{Mono}) or biphasic (PFA_{Bi}) waveforms to standard radiofrequency ablation.

METHODS

The data, analytic methods, and study materials will not be made available for purposes of reproducing the results or replicating the procedure.

All preclinical experiments were approved by the Institutional Animal Care and Use Committees at the Mount Sinai Hospital, NY. A total of 14 female Yorkshire swine (60–70 kg) were included in the PFA group and 3 swine in the control radiofrequency group. The monophasic experiments preceded the biphasic experiments, and therefore randomization was not performed. Sample size was not calculated as this was the first time this energy was being studied.

Procedural Details

The swine were premedicated, intubated, and mechanically ventilated with isoflurane (1%–3%) after an overnight fast. Percutaneous femoral venous access was then obtained, and single transseptal puncture was performed for left atrial access after systemic heparin administration. A deflectable sheath was used for all ablation in both groups. A circular mapping catheter was placed in the right superior PV (RSPV), inferior common PV (ICPV), and superior vena cava (SVC) to evaluate electrograms both at baseline and at the follow-up to assess for electric isolation. All swine also had venous access to allow for coronary sinus, right ventricular apical catheter placement as well as intracardiac echocardiography.

In the study group, ablation was performed using a custom, programmable PFA generator, a PFA catheter and a 13-French steerable sheath to navigate and position the PFA catheter (Farapulse, Inc; Menlo Park, CA). The custom generator is capable of delivering a high-voltage pulsed field waveform over multiple channels, and the 12-F over-the-wire PFA ablation catheter (Farawave, Farapulse) has 5 splines, each containing 4 electrodes. Electrode size and spacing are comparable to commercial diagnostic catheters (Figure 1). When fully deployed, the diameter of the distal portion is 31 mm. The catheter was advanced over a guidewire such that the splines achieve circumferential contact/proximity with the PV antra. All biphasic and monophasic PFA applications were delivered in bipolar fashion between catheter electrodes, and no ground pad was used. In addition, all PFA deliveries were between pairs of electrodes, and all electrodes were employed in the course of a delivery. The catheter was positioned to ensure circumferential PV ostial and antral coverage. Arcing during PFA delivery is avoided through a proprietary process incorporating optimization of the catheter design including electrode size and spacing, pulse duration and voltage amplitude.[2,3]

The splines were positioned to ensure symmetrical coverage and contact as assessed on fluoroscopy and intracardiac echocardiography. The catheter was placed in the SVC and both PVs based on intracardiac echocardiographyand fluoroscopic guidance. The PFA waveforms consisted of a sequence of microsecond-scale pulses at amplitudes from 800 V (PFA_{Mono}, 7 swine) to 1800 V (PFA_{Bi}, 7 swine). Both waveforms were delivered over 4 (PFA_{Mono}) or 10 (PFA_{Bi}) heart beats with the catheter fully deployed in its flower pose (Figures 1 and 2). Pulses were synchronized to joint pacing from the CS catheter and the RV apical catheter via a Micropace stimulator. In the PFA_{Mono} group, a fast-acting, short-duration paralytic was given intravenously as required during the ablation sequence to minimize skeletal motion in the porcine model. In the PFA_{Bi} group, no paralytic was administered as skeletal muscle capture did not occur. All swine underwent phrenic nerve pacing from the SVC before ablation and in follow-up. In select swine, venous angiography and coronary angiography were performed at baseline, immediately after ablation and in follow-up.

In the radiofrequency group, the RSPVs and SVCs were circumferentially ablated using interrupted, point-by-point ablation technique targeting 35 Watts with a contact force-sensing, 3.5 mm irrigated ablation catheter and power-controlled generator (Biosense Webster). ICPVs were not attempted due to manipulation difficulty in the constrained

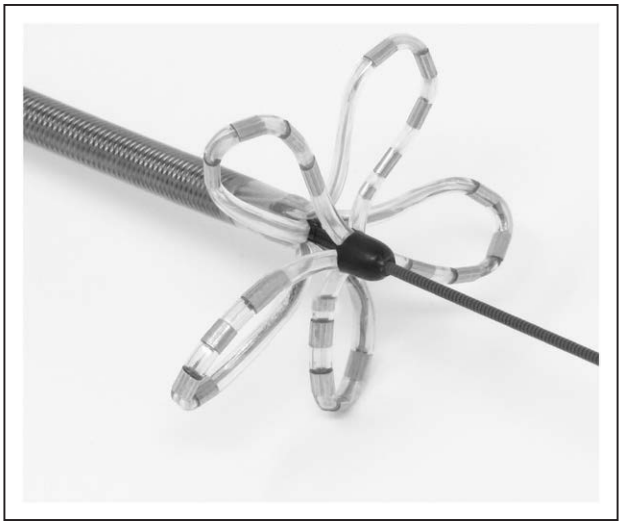

Figure 1. Multielectrode pulsed field ablation catheter deployed in flower pose.

porcine model. Saline flow rate of 17 mL/min was used in the left atrium and 5 mL/min in the right atrium. The maximal duration and electrode temperature of each radiofrequency application was set to 30 seconds and 42°C, respectively. Electroanatomic maps (Carto3 V4 System, Biosense Webster) were created in animals using either a circular multipolar mapping catheter or a 3.5 mm tip ablation catheter to appreciate the region of low voltage in select swine in both groups.

The animals were recovered and brought back for a repeat procedure at ≈2 months. During these procedures, one swine developed an acute pneumothorax likely related to intubation and ultimately expired due to hypoxic arrest. Venous diameters were assessed in select animals by performing venous angiography in similar fluoroscopic view. Offline measurement was performed using quantitative vascular analysis, and phrenic nerve function was confirmed by pace capture at 10 mv at 2 ms output via a 3.5 mm tip catheter from the SVC. All swine were then humanely euthanized. The hearts were then submitted for histopathologic examination.

Histological Investigation

All specimens were fixed in formalin. Veins were opened along their long axes, and longitudinal sections along the same axes were obtained and processed. All tissues were stained with Hematoxylin and Eosin and with Masson's Trichrome staining. The objectives of the histology portion of this study were to evaluate the sections of vein with myocardial sleeve for lesion presence and transmurality; viability of nerves, arterioles, and venules within the lesion; the presence of edema; the presence of thrombi and the chronicity of the thrombi if present; and any other relevant findings. Myocardial thickness measurements for sections with a lesion were taken within the remaining myocardium adjacent to the lesion when present (see black line in the figure). For sections with no lesion, the myocardial thickness measurement was taken at the center of the myocardial tissue section. When the lesion was transmural across the myocardium, the thickness measurement was taken at the center of the transmural area. If the lesion was not transmural, the thickness measurement was taken at the center of the lesion. Several additional variables were analyzed such as fibrosis, inflammation, hemorrhage, arteriolar, venular, and nerve damage etc.

Statistical Analyses

Study results are presented using descriptive statistics. For continuous variables, the results include number, mean, SD where pertinent. They were compared using paired *t* test or ANOVA, as appropriate. Presented data for categorical variables includes the number and percent in each category and were compared using χ^2 analysis or Fisher's test, as appropriate. Statistical analyses were performed with SPSS 23.0 software (SPSS Inc, Chicago, IL).

RESULTS

Acute Experiments

The mean weight of swine at the time of acute experiments was 56.3±6.3 kg with no difference between cohorts.

PFA Cohorts

PFA was successfully delivered to 40 veins, for a total PFA delivery time of <1 min/animal (Table 1, Figure 2A through 2C). No applications resulted in waveform discontinuities suggestive of arcing. Immediate microbubble formation was visible with PFA on intracardiac echocardiography and rapidly resolved. No notable arrhythmias occurred with any PFA deliveries. One episode of sinus bradycardia persisted for 2 hours but was attributable to mechanical effects, occurring after catheter manipulation but before therapy. Sinus rates were mildly tachycardic for brief periods (<1 minute) after some monophasic PFA deliveries and rapidly resolved. No other atrial or ventricular arrhythmias were noted.

In the SVC, the PFA catheter was placed without concern for phrenic nerve proximity, and continuous phrenic pacing from a different catheter/location was not performed during PFA delivery. The phrenic nerve was, however, captured by the PFA pulses during pulse delivery in the RSPV and SVC. After PFA delivery, phrenic nerve function was demonstrated to be preserved by pacing, as there was no diminution of diaphragmatic excursion or obvious increase in pacing thresholds. In both PFA cohorts, evaluation of electrical isolation was unequivocal with an appreciable lack of confounding far-field electrograms following deliveries.

Monophasic Cohort

In 7 swine, all targeted veins, including 13 PVs (7 RSPVs and 6 ICPVs) and 7 SVCs, were successfully isolated at first pass (Table 2, Figure 2D). The ICPV in one swine was not targeted because of difficulty accessing the venous ostium, which was located close to the transseptal access site. Monophasic PFA deliveries were associated with skeletal muscle and diaphragmatic stimu-

Table 1. Acute and Chronic Vein Isolation Rates Between Cohorts

	Monophasic (n=7)			Biphasic (n=7)			RF (n=3)			*P* Value
Acute vein isolation	7/7 SVC; 13/13 PV			6/6 SVC; 14/14 PV			3/3 SVC; 3/3 PV			n/a
All veins	20/20 (100%)			20/20 (100%)			6/6 (100%)			n/a
Durable vein isolation	1/7 SVC; 9/11 PV			6/6 SVC; 12/12 PV			1/3 SVC; 2/3 PV			*P*=0.008 for SVC; *P*=0.154 for PV
All veins	10/18 (55.6%)			18/18 (100%)			3/6 (50%)			*P*=0.002
Phrenic palsy	0/20			0/20			0/6			n/a
Venous stenosis	0/7			0/7			0/6			
Pairs of veins analyzed	n=13			n=9			n=4			
	Pre: 15.8±2.7	Post: 15.8±3.5	*P*=0.99	Pre: 17.0±3.4	Post: 17.2±3.8	*P*=0.62	Pre: 16.4±1.6	Post: 13.1±2.3	*P*=0.015	

Incidence of phrenic nerve palsy and venous stenosis between baseline and follow-up time points. PV indicates pulmonary vein; RF, radiofrequency; and SVC, superior vena cava.

lation, resulting in significant animal movement and requiring administration of paralytics.

Immediately post-delivery, hemodynamically insignificant ST elevation and T wave peaking were frequently observed, but these changes rapidly resolved completely without intervention. Coronary angiography was performed concurrent to PFA in one swine—the transient ST-T changes were not associated with any evidence of coronary spasm. Repolarization changes were typically more prominent in the precordial leads during RSPV and SVC applications, and in the inferior limb leads during ICPV applications (Figure 3).

Biphasic Cohort

Similar to monophasic PFA, all targeted PVs in 7 swine, including 14 PVs (7 RSPVs and 7 ICPVs) and 6 SVCs, were successfully isolated at first pass. (Table 1). The SVC was not targeted in one swine due to an enlarging groin hematoma that threatened animal survival. In contrast to monophasic applications, muscular engagement was significantly reduced with biphasic PFA, so paralytic agents were not required. Furthermore, repolarization changes were observed to be insignificant during biphasic delivery.

Radiofrequency Cohort

In 3 swine, all of the 3 targeted RSPVs were isolated by point-by-point radiofrequency ablation; the ICPV was not targeted due to difficulty in placing these circumferential lesions in the constrained swine model. Mild acute PV narrowing was appreciated on RSPV venography performed immediately post-ablation (Fig-

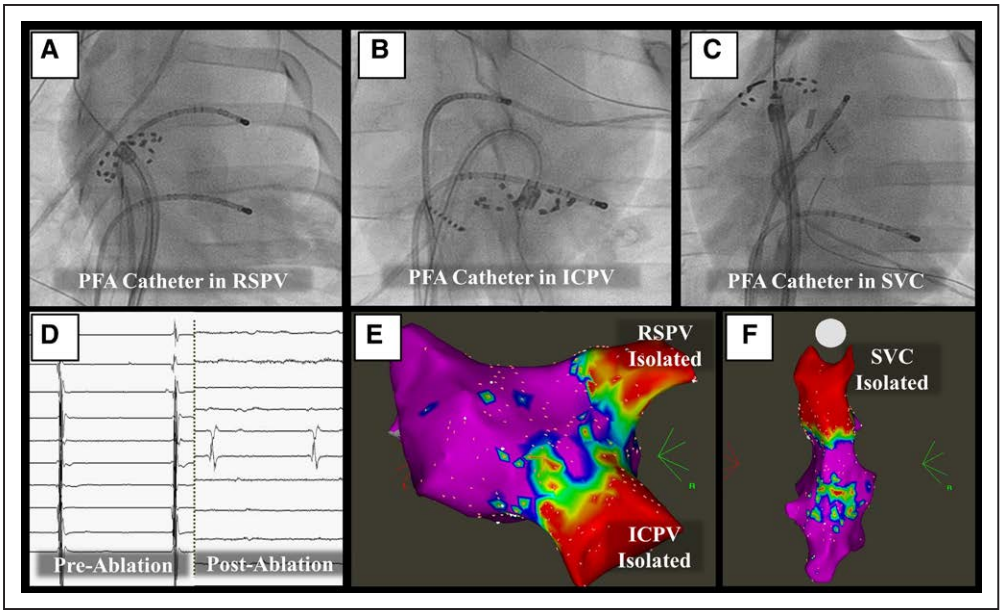

Figure 2. Catheter based pulsed field ablation (PFA).
A–**C**, PFA catheter deployed over-the-wire in right superior pulmonary vein (RSPV), inferior common pulmonary vein (ICPV), and superior vena cava (SVC) of swine through a deflectable sheath. Pacing catheters are placed in the coronary sinus and the right ventricular outflow tracts. **D**, Baseline and post-ablation (after survival) pulmonary vein electrograms from a multipolar circular catheter. **E** and **F**, Voltage maps performed at follow-up showing level of isolation in the RSPV, ICPV, and SVC.

Table 2. Section Transmurality, Lesion Distribution, Myocardial, and Lesion Thickness Between PFA Waveforms and RF Cohorts

		Mono	Bi	RF	*P* value	Mono vs Bi	Mono vs RF	Bi vs RF
SVC	Lesion present	57/65	51/57	22/23	0.559			
	Transmurality	52/57	51/51	21/22	0.079			
	Myocardial thickness, mm	1.16+0.65	0.77+0.45	1.47+0.41	<0.001	<0.001	0.051	<0.001
	Lesion thickness, mm	0.79+0.76	0.46+0.43	1.31+1.06	<0.001	0.015	0.111	0.004
RSPV	Lesion present	45/48	45/50	19/19	0.382			
	Transmurality	40/45	34/45	17/19	0.174			
	Myocardial thickness, mm	1.98+1.53	1.56+1.13	2.02+1.37	0.239	0.279	0.994	0.425
	Lesion thickness, mm	0.99+0.70	0.87+0.83	1.76+1.61	0.152	0.731	0.225	0.148
ICPV	Lesion present	54/68	56/69	n/a	0.797			
	Transmurality	46/54	53/56	n/a	0.098			
	Myocardial thickness, mm	1.39+0.75	1.50+1.05	n/a	0.464			
	Lesion thickness, mm	0.74+0.48	0.96+0.69	n/a	0.059			
All	Lesion present	156/181 (86.2%)	152/176 (86.4%)	41/42 (97.6%)	0.110			
	Transmurality	138/182 (75.8%)	138/152 (90.8%)	38/41 (92.7%)	0.657			
	Myocardial thickness, mm	1.46+1.04	1.28+0.99	1.72+1.00	0.030	0.219	0.308	0.035
	Lesion thickness, mm	0.83+0.66	0.76+0.69	1.49+1.30	0.007	0.653	0.015	0.007

The denominator in the first row of each section represents the total number of vein sections (longitudinal along the long axis of the PV) that were submitted for analysis with the numerator describing the number of sections that demonstrated evidence of lesions. In the second row, the denominator represents only those sections that demonstrated lesions, whereas the numerator describes those that were transmural. ICPV indicates inferior common pulmonary vein; PFA, pulsed field ablation; RF, radiofrequency; RSPV, right superior pulmonary vein; and SVC, superior vena cava.

ure in the Data Supplement). SVC encirclement was not completed in 2 of 3 swine to spare the phrenic nerve; however, electrical SVC isolation occurred in all 3 swine. Phrenic nerve capture was preserved post-radiofrequency ablation in all swine. There were no arrhythmias or repolarization changes.

Survival Experiments: Remapping Study

All swine completed the follow-up period. There was an average 30.1% increase in weight after a mean survival of 63±3.3 days.

PFA Cohorts

For the PFA_{Bi} group, 12/12 (100%) PVs and 6/6 (100%) SVCs were durably isolated. For the PFA_{Mono} group, 9/11 (82%) PVs and 1/7 (14%) SVCs were durably isolated. In this group, confident electrical isolation re-assessment was difficult in 2 of 6 inferior common veins: accordingly, both of these veins were excluded from PV isolation analysis (Table 1), (Figures 2E, 2F, and 4).

For both PFA cohorts, right phrenic nerve function was intact in all (100%) swine. Venous angiography did not reveal any luminal transitions to suggest vein stenosis. Right and left coronary angiography, performed in all swine at baseline and follow-up, did not reveal any evidence of luminal irregularities or stenosis. Gross review of left ventricular function via intracardiac echocardiography did not demonstrate any wall motion abnormalities and suggested normal function. There were no abnormal repolarization changes noted on EKG during follow-up.

Radiofrequency Cohort

Only 1/3 (33%) SVCs and 2/3 (67%) RSPVs remained electrically isolated at follow-up. There was a statistically significant reduction in PV diameters at follow-up in this cohort (from 16.4±1.6 mm to 13.1±2.3 mm, P= 0.015). Phrenic nerve capture was preserved in all swine.

Histological Investigation

Lesions were easy to appreciate in most specimens on gross examination. PFA lesions demonstrated a pale appearance with distinct margins consistent with their chronic nature. In the SVC samples within the PFA_{Mono} cohort, a visual gap (Figure 4A) could be appreciated within the circumferential lesion set in 4 of 7 specimens; SVC visual gaps did not occur in the PFA_{Bi} specimens but were present where the phrenic nerve was avoided in radiofrequency specimens. Overall, PFA lesion boundaries (Figure 4A) reflected the catheter position within the ablated structures and a confluent, wide zone of ablation was easy to appreciate especially in the PFA_{Bi} specimens (Figure 4B and C).

Histological parameters such as transmurality and lesion thickness at the SVC, RSPV, and ICPV are shown for the PFA_{Mono}, PFA_{Bi}, and radiofrequency arms (Table 2). Overall the majority of lesions in all cohorts were transmural without statistically significant differences (PFA_{Mono}, 75.8%; PFA_{Bi}, 90.8%; and radio-

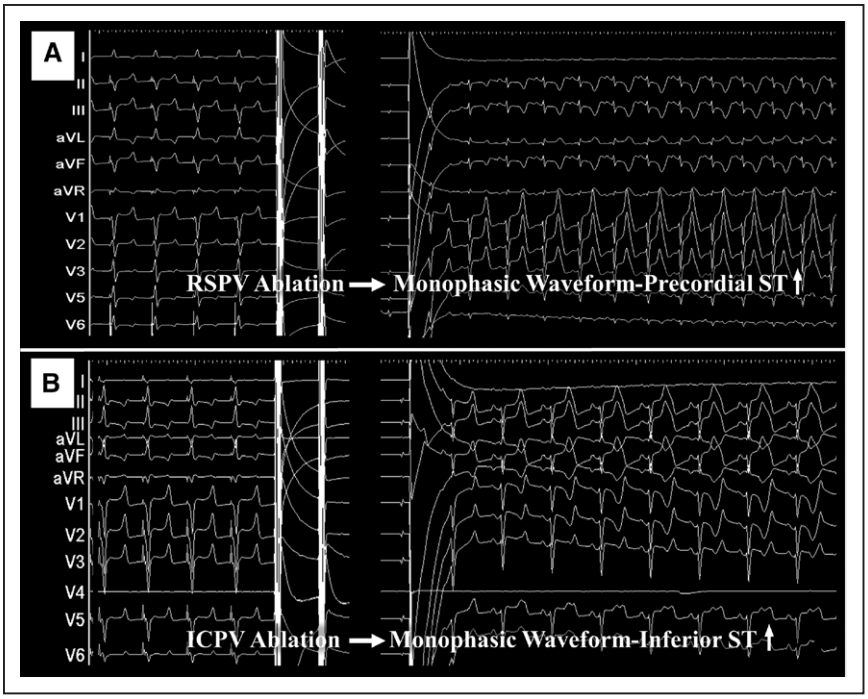

Figure 3. Twelve lead EKGs demonstrating transient repolarization changes.
A, Right superior pulmonary vein (RSPV) ablation with artifact of pulsed field ablation (PFA) pulse, followed by ST elevation in the precordial leads. **B**, Inferior common pulmonary vein (ICPV) ablation followed by ST elevation in inferior leads.

frequency, 92.7%; *P*=NS). The tissue was significantly thicker in the SVC sections of the PFA_{Mono} and radiofrequency arms, consistent with more proximal catheter placement in these groups.

The PFA lesions were composed of organized, homogeneous fibrosis replacing the myocardium (Figure 5A through 5C) with well-demarcated border zones consistent with their gross appearance. Interestingly, at their center, the PFA lesions were thinner than the adjacent unablated myocardium—possibly a result of the more organized and layered collagenous deposition attendant with PFA. In radiofrequency lesions, fibrosis was disorganized and heterogeneous, and mononuclear cellular infiltration was present to a higher degree, consistent with a greater inflammatory response.

In the PFA cohorts, nerves were observed without any evidence of damage and preserved without fibrotic infiltration, nor was there any evidence of thrombus (Figure 5A through 5D). In contrast, the radiofrequency cohort demonstrated lesions that contained damaged nerve cells, all noted within SVC sections. In four of these sections, the damaged nerve was within the central myocardium and in one section, the damaged nerve was observed adjacent to the epicardium. There was mild to moderate fibrosis and loss of the nerve fascicles in these nerves (Figure 5E and 5F). Finally, PFA had no appreciable effect on arterioles and venules despite being surrounded by fibrotically replaced myocardium. Arteriole damage was also not observed with radiofrequency energy.

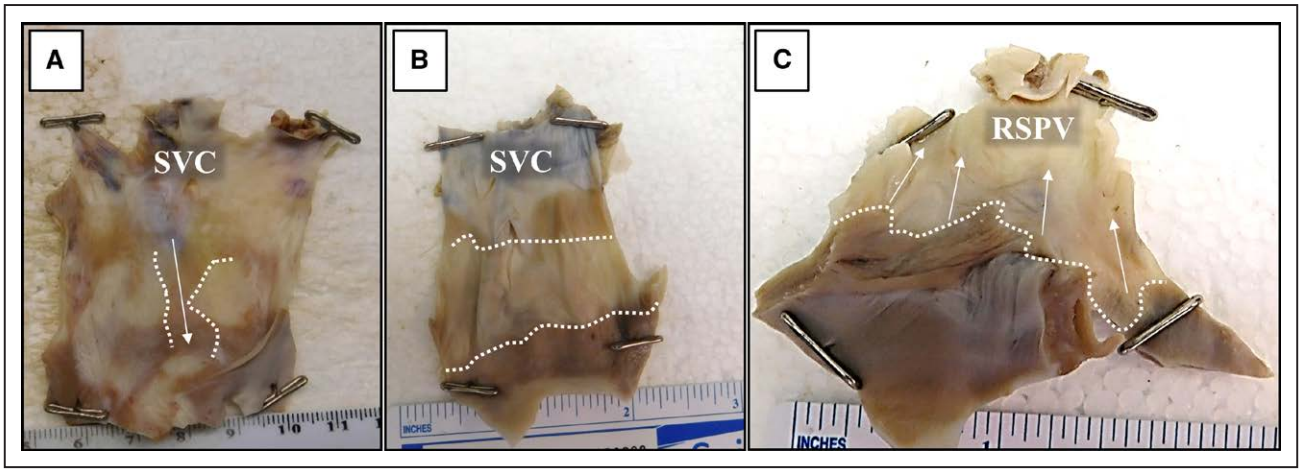

Figure 4. Gross appearance of pulsed field ablation (PFA) lesions seen after formalin fixation.
A, Monophasic PFA lesion in the superior vena cava (SVC) with presence of a visual gap (arrow). **B**, Biphasic PFA lesion in the SVC with contiguous and broad lesion (between dotted lines). **C**, Biphasic PFA lesion in the right superior pulmonary vein (RSPV) with contiguous broad lesion (arrows point in direction of distal pulmonary vein).

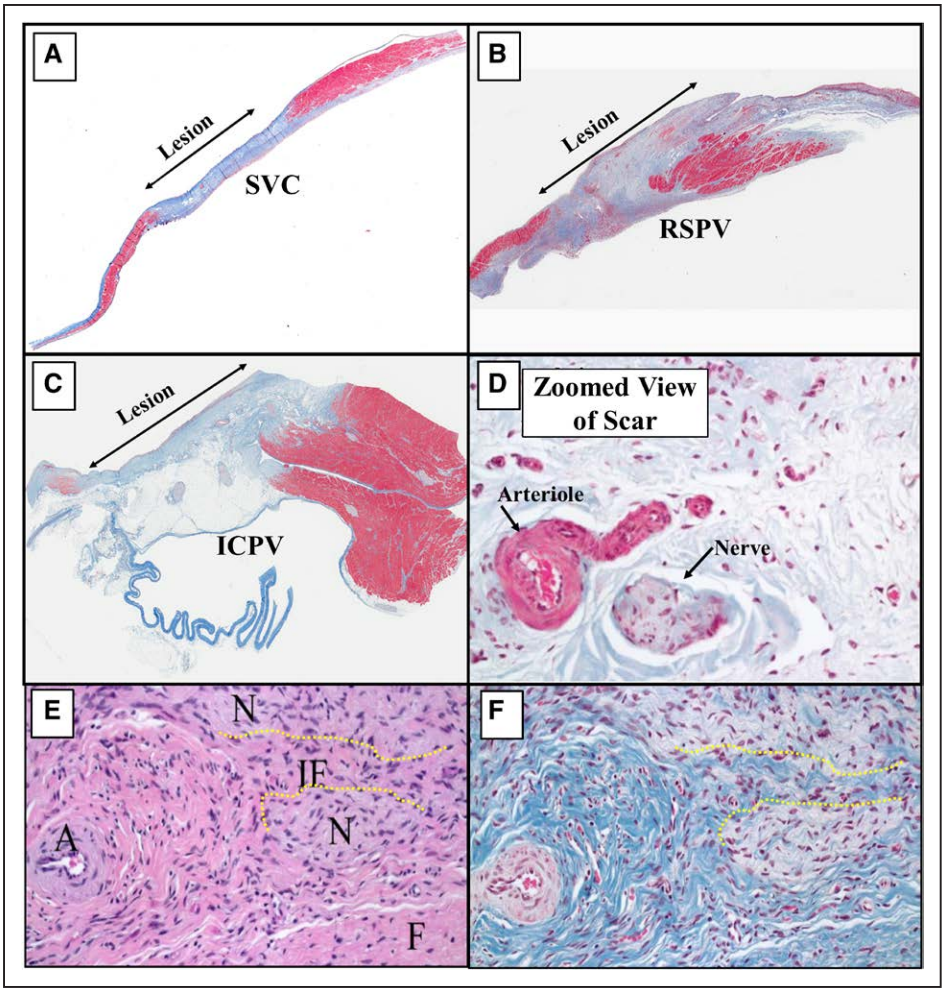

Figure 5. Masson's trichrome stain of sections from Biphasic cohort.
A, Transmural pulsed field ablation (PFA) lesion in the superior vena cava (SVC; 10× magnification). **B**, Transmural PFA lesion in the right superior pulmonary vein (RSPV). **C**, Transmural PFA lesion in the inferior common pulmonary vein (ICPV). **D**, 200× view of fibrotic core of PFA—SVC lesion demonstrating a spared arteriole and nerve surrounded by fibrosis. **E/F**, 200× view of fibrotic core of radiofrequency (RF)-SVC lesion demonstrating a normal arteriole and a nerve infiltrated by fibrosis. **E**, Hematoxylin and Eosin; and **F**, Masson's trichrome. A indicates arteriole; F, fibrosis; IF, infiltrating fibrosis in nerve (dotted lines); and N, nerve.

DISCUSSION

In this in vivo survival study, we demonstrate the efficacy and safety of achieving electrical isolation using optimized monophasic and biphasic PFA waveforms. Specifically, we observed favorable safety and durability of lesions with the newer biphasic waveform, describe important procedural characteristics of PFA in the swine model, and provide histological assessments of the treated myocardium. In particular, both PFA waveforms created confluent myocardial lesions while avoiding PV stenosis and sparing inlying and adjacent structures, particularly nerves. Finally, we provide comparative data between the 2 PFA waveforms and radiofrequency ablation.

Electric fields generated during PFA have been shown to create cell death by irreversible electroporation. Myocardial cells have a lower threshold for irreversible electroporation than cell types associated with collateral damage such as nerves, arteries, and the esophagus as seen in the clinical setting.[6–9] This uniquely tissue-selective basis of lesion formation differs from contemporary thermal energy sources such as radiofrequency, which effects coagulative necrosis of all structures within a lethal thermal zone. This is particularly relevant for AF ablation where complications such as phrenic palsy, PV stenosis, and esophageal injury seem to be inexorably linked to strategies that aim to improve ablation efficacy.

Such advantages of PFA have been corroborated by several preclinical studies.[10–13] However, the majority of these studies used a monopolar and monophasic delivery from an external defibrillator repurposed without optimization for endocardial ablation. With this approach, these authors successfully demonstrated the feasibility of achieving irreversible electroporation of porcine PV ostia. In their chronic swine series, they delivered shocks using a circular multielectrode catheter and demonstrated reduced PV electrogram amplitudes and increased pacing thresholds, with histological lesions as deep as 3.5 mm. But due to design limitations of the catheter, they did not attempt to isolate veins and were

not able to report on lesion durability. More recently, biphasic PFA using a multipolar catheter was shown to create confluent lesions in atrial tissue in a preclinical study, but no attempts were made to pursue electrical end points such as vein isolation or conduction block.[14]

In the present series, we add to the understanding of endocardial PFA in atrial myocardium by demonstrating that relevant electrophysiological end points such as durable electrical isolation can be achieved with excellent safety and observable tissue selectivity. These data are in support of the expanding clinical experience with this PFA system.

Indeed, we demonstrated that the biphasic waveform achieved superior durability compared with the monophasic and radiofrequency cohorts for targeted veins: 18/18 (100%) versus 10/18 (55.6%), and 3/6 (50%; P=0.002), respectively—an observation replicated in the clinical experience. From a histological perspective, there were no significant differences between sections with lesion present and transmurality rates between all groups. Limited sample size and sectioning techniques may be responsible for the statistical equivalence in histological assessment, which runs counter to the variance in durable isolation rates. The transmurality rates were numerically lower in the mono versus bi group (75.8% versus 90.8%). The differences in durable isolation rates between the PFA_{Mono} and PFA_{Bi} groups was driven by the asymmetrically low rates of durability of the SVC in the PFA_{Mono} cohort (Figure 4). This could be partly explained by the more proximal (SVC-right atrial junction) positioning of the PFA catheter in this cohort, thereby leading to reduced catheter–SVC wall contact during phrenic activation at this location. Indeed, this proximal positioning is reflected by the presence of thicker sections noted in the SVC specimens in this cohort (Table 2). Other explanations include an actual reduced efficacy of the PFA_{Mono} waveform and operator learning curve as the PFA_{Bi} experiments were performed subsequent to the PFA_{Mono} experiments.

Despite the differences in lesion durability, acute isolation was easily and universally achieved with both PFA waveforms. This experience suggests that the divergence between acute and durable electrical isolation, certainly an observation with thermal ablation, maybe even more striking with PFA.

The interaction between efficacy and safety was on full display during SVC ablation. The proximity of the phrenic nerve did not impede PFA applications at the SVC; in contrast, full encirclement with radiofrequency ablation lesions was not attempted in 2 of 3 SVCs to avoid jeopardizing animal survival with diaphragmatic paralysis. While PFA_{Bi} and PFA_{Mono} lesions left the phrenic nerves intact, radiofrequency damaged nerves in 5 SVC locations despite employing avoidance maneuvers common to clinical practice. Similarly, there was a statistically significant ≈20% reduction in venous diameters in the radiofrequency group that was not seen in either PFA group. This, coupled with the lack nerve damage with PFA, highlights the tissue selectivity of this PFA system with reduced or absent risk of PV stenosis and phrenic nerve injury. Importantly, these putative safety benefits were also observed in the human clinical experience.[1]

Finally, PFA lesions were consistently homogeneous, with a layered fibrotic infiltration, no sequestered myocytes, and a clear border zone. In contrast, radiofrequency lesions demonstrated a consistent pattern of disorganized fibrosis.

Although a fixed waiting period was not routinely used; there were no early reconnections noted. Characteristically, there is significant reduction even of the farfield atrial signals on the multipolar catheter. Muscular and diaphragmatic activation was significantly more pronounced with the monophasic than with the biphasic waveform—obviating the need for neuromuscular paralysis with the latter waveform. This important workflow advantage was also realized in the recent clinical evaluation.[1] Overall muscular contractions qualitatively appear to be more pronounced in the swine model than what was observed in the first-in-human studies.

Observable repolarization changes after PFA were prominent with the monophasic waveform and minimal with the biphasic waveform. These changes rapidly resolved and were not associated with blood pressure changes. Repolarization changes, however, were not observed clinically, suggesting that this could be specific to the swine-model in which PVs and ventricular myocardium are more closely positioned. The near simultaneous onset of these changes to the pulse delivery (Figure 3) suggest that the mechanistic basis is likely an electrical phenomenon and not related to coronary ischemia. Indeed, when angiography was performed concurrent to PFA delivery, no coronary spasm was observed. Microbubble formation was short-lived, and although its effects on end organs was not assessed in this study.[1]

Limitations

The safety and durability seen in this experiment is promising, but any interpretation must be made keeping the small sample size in mind, in particular the radiofrequency arm where the number of swine was 3 as opposed to 7 each in the PFA arms. The tissue specificity of PFA can be altered with even small changes to delivery parameters, including waveform composition and catheter electrode design and configuration; accordingly, the results described herein cannot be assumed to be applicable to other PFA systems. The waveforms tested in this study are identical to 2 of those evaluated in a clinical study, with the biphasic waveform receiving subsequent incremental optimization.[1–3]

Conclusions

PFA-based vein isolation using the waveforms and device in this study was feasible, safe, and demonstrated a myocardial-specific ablative effect. PFA spared nerves and caused no PV narrowing while radiofrequency did not. Biphasic PFA lesions were more durable than monophasic PFA and radiofrequency ablation.

ARTICLE INFORMATION

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